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13. ABSTRACT (Maximum 200 Words) The schweinfurthins are natural products first isolated from an African plant. Two of these compounds, Schweinfurthins A and B, have demonstrated a unique pattern of cytotoxicity in the NCI's 60 cell line panel, and breast cancer cell lines such as MCF7 and HS 578T were among the more sensitive. To study the basis of the unique activity of these compounds, and to develop a more reliable source, a chemical synthesis has been initiated. These efforts have led to preparation of Schweinfurthin C, the inactive congener, by a synthetic strategy centered on a right half subunit that also can be employed in synthesis of Schweinfurthins A and B. Two routes have been explored for preparation of the required left half of the bioactive compounds. The more advanced route is based on the cationic cyclization of a monocyclic precursor to a tricyclic target. The key cyclization step has been accomplished, demonstrating the viability of our approach and yielding an advanced intermediate for synthesis of these complex natural products. At the same time, routes to modified right half subunits are under investigation, to obtain analogues of the natural product that can be used in studies of the mechanism(s) responsible for the biological activity.				
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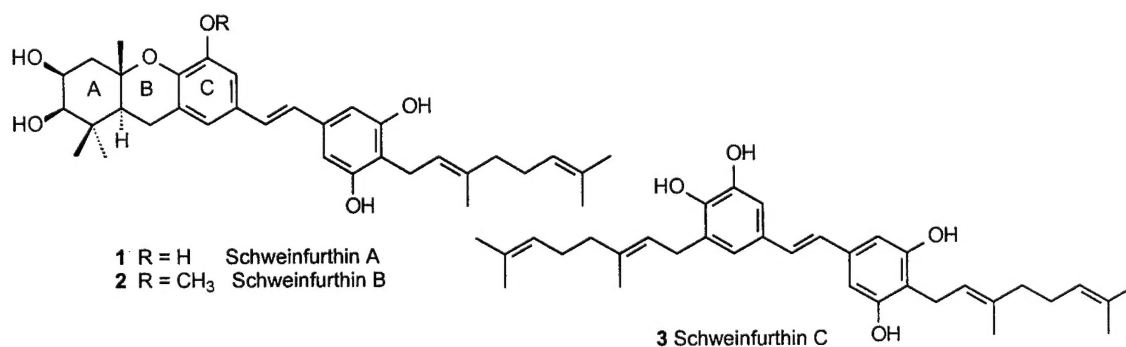
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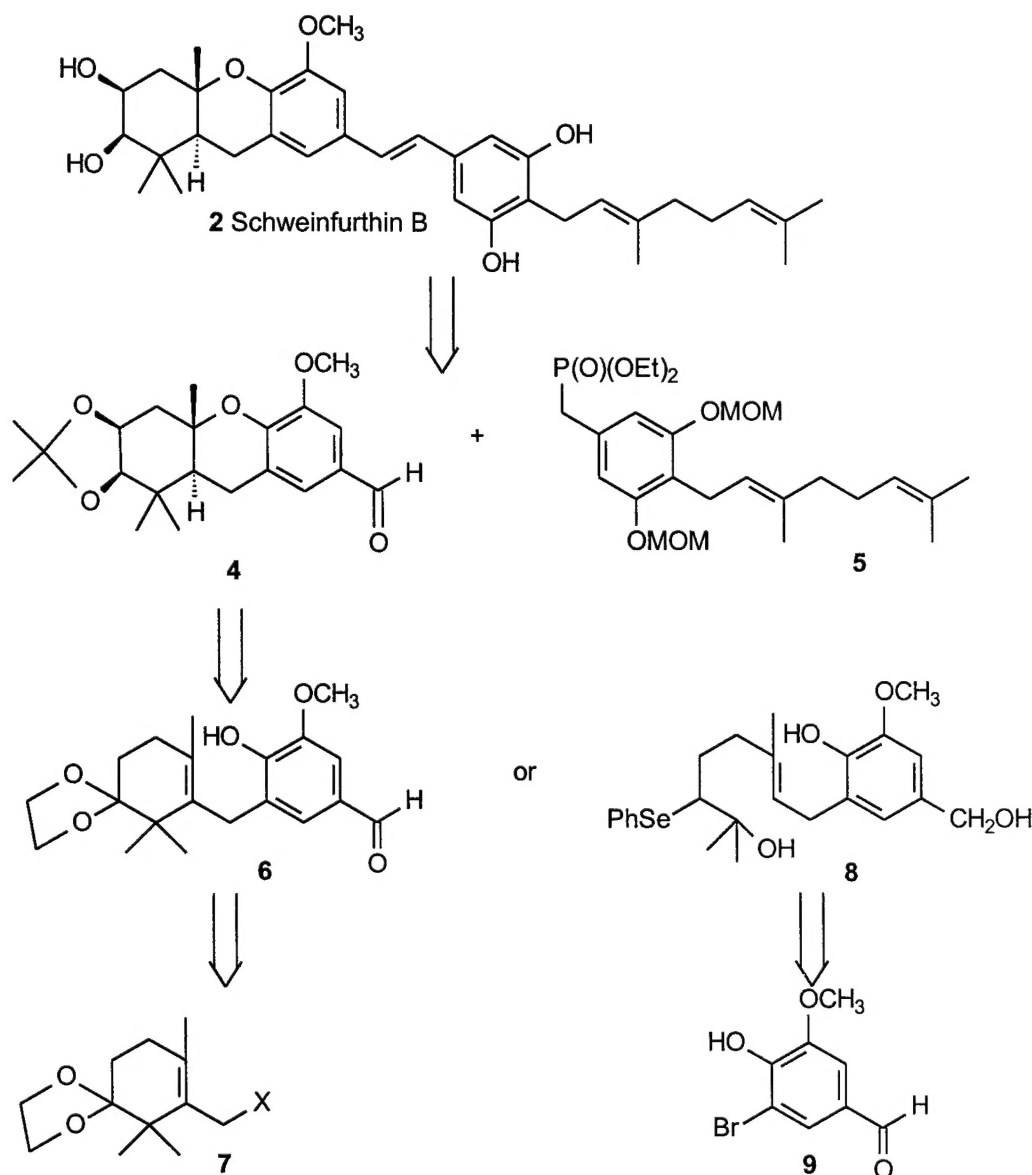
Introduction.

In 1998, three novel compounds (**1-3**) were isolated from a plant extract as part of the National Cancer Institute's (NCI) search for potential anticancer agents from natural sources.¹ Two of the compounds, schweinfurthin A and B, demonstrated significant cytotoxicity in the NCI's 60 cell line panel. Among the more sensitive lines were the breast cancer cell lines MCF7 and HS 578T, but even more intriguing was the overall pattern of activity. Sensitive cell lines differed substantially in many key characteristics, including in vitro doubling time, DNA repair phenotype, and MDR status. Statistical analysis suggests that the schweinfurthins act at a cellular or molecular target different from any current clinical agent, and also different from all but two much more complicated compounds in the NCI database. The combination of significant activity and a unique mode of action represents a promising lead for breast cancer therapy. Unfortunately, the original natural source, the African plant *Macaranga schweinfurthii* Pax., has proven to be an unreliable source of these compounds and repeated efforts to secure more material through reisolation have met with very limited success.² Therefore, to obtain a more reliable source of these natural products, and to allow access to analogues designed to probe the basis of the biological activity of these compounds, we have undertaken a chemical synthesis of the schweinfurthins.

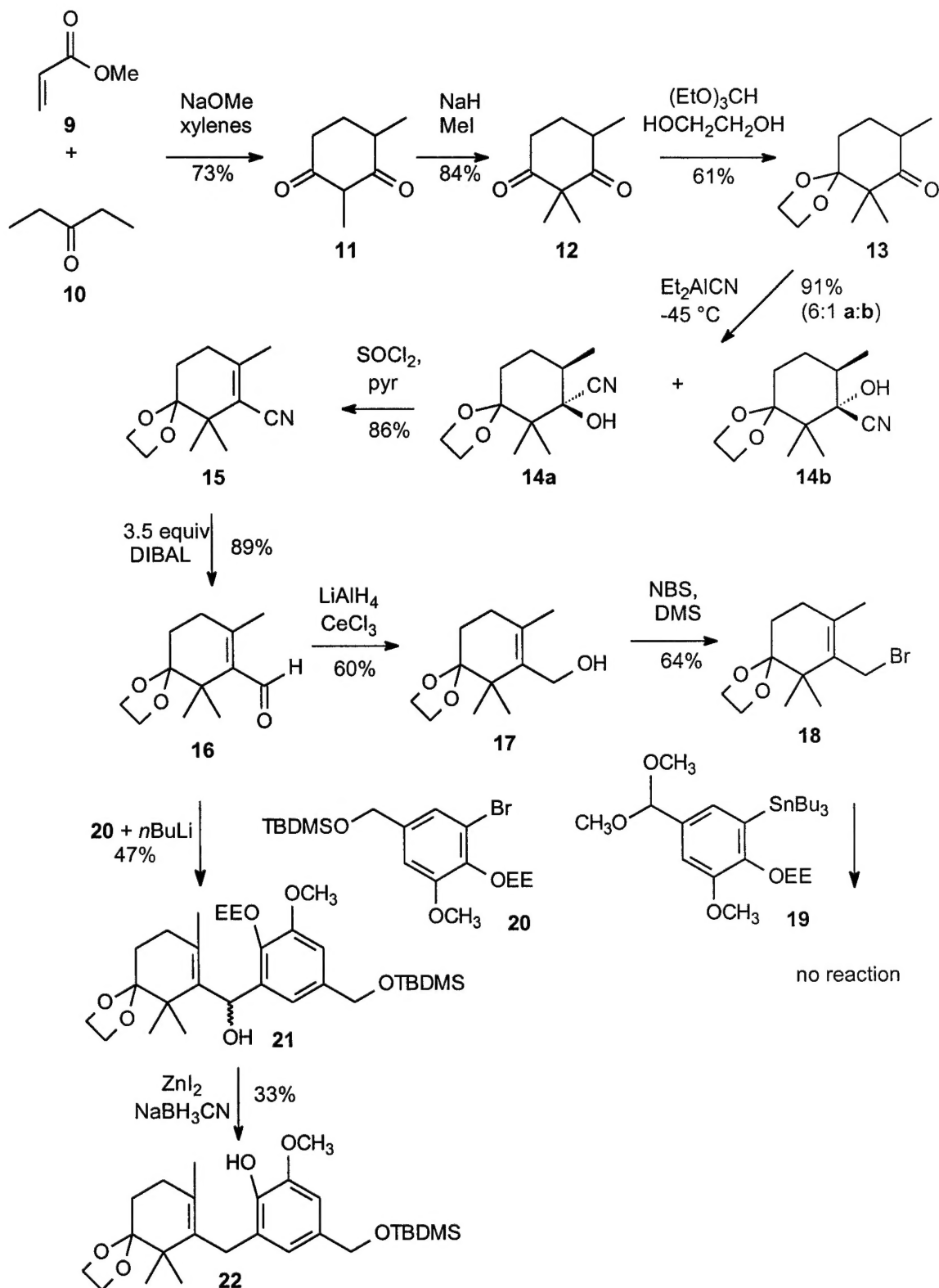


Body.

Schweinfurthin B (**2**) is our primary synthetic target. As shown below, our synthetic strategy is based on a convergent approach where two subunits of approximately equal complexity are joined in formation of the central stilbene olefin. The "right half" section required for this strategy is the phosphonate **5**, which we already have prepared and used in preparation of Schweinfurthin C,³ the least complicated but inactive member of this family. Therefore, we have focused our efforts on preparation of the "left half" subunit for Schweinfurthin B, the tricyclic aldehyde **4**. Two routes have been explored for preparation of aldehyde **4**. The first would involve construction of a cyclohexenyl intermediate to represent the A-ring of the target (e.g. compound **7**), linkage of the A-ring intermediate to an aromatic system representative of the C-ring to give a bicyclic product (e.g. compound **6**), and then ring-closure to afford the central B-ring. The alternative route envisioned construction of a C-ring bearing a 10-carbon chain (e.g. **8**) that could be cyclized to afford the A- and B-rings in a single cascade process.

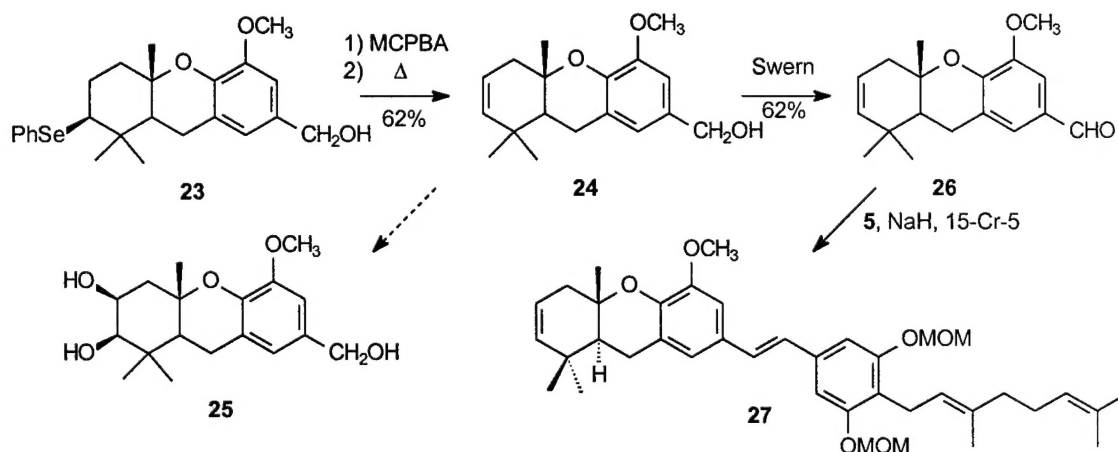


As summarized in the following scheme, we were able to prepare the allylic bromide **18**, which corresponds to one specific form of structure **7**. While it proved difficult to join this bromide to an aromatic precursor to the C-ring (**19**), we were able to bring about condensation of a C-ring precursor (**20**) with the intermediate aldehyde **16**. Unfortunately, selective reduction of the resulting allylic alcohol in the presence of the benzylic alcohol also proved difficult. Given the low yields at several steps in this sequence, more attention has been focused on the alternate route to the tricyclic aldehyde **4** via the monocyclic precursor **8** and this route has proven more successful. Because both the preparation of compound **8** and its cyclization to the tricyclic product **23** are described in a submitted manuscript (Appendix), details of this sequence will not be included here. Instead this report will summarize subsequent transformations of the initial tricycle **23**.

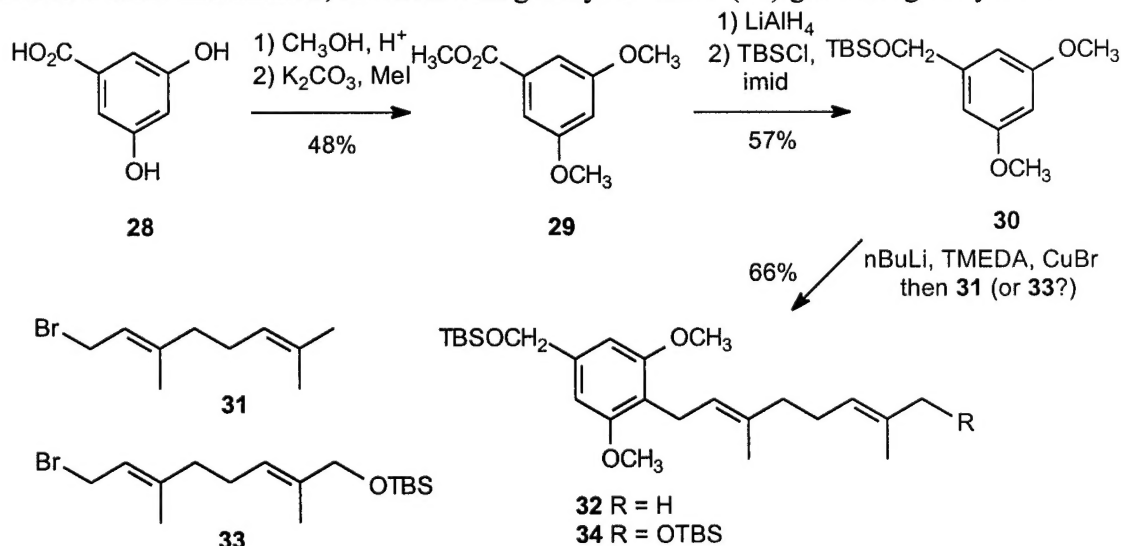


Compound **23** is now available through an 11-step sequence from commercial vanillin in ~10% yield, as described in the Appendix. This compound has been converted

to the corresponding olefin **24** through a standard oxidation–selenoxide elimination sequence. We are currently exploring oxidation of this olefin to introduce the diol functionality necessary in an intermediate leading to the natural product (i.e. **25**). Because it may prove difficult to introduce the diol with the desired stereocontrol, compound **24** also has been oxidized to the tricyclic aldehyde **26**, and then treated with the right half phosphonate **5** to obtain the protected dideoxyschweinfurthin **27**. After hydrolysis of the MOM protecting groups, we should obtain a schweinfurthin analogue and that product will be sent to our collaborators for bioassays. If the dideoxyschweinfurthin analogue would show biological activity comparable to that of the natural product, it could be used to probe the mechanism(s) which underlie the biological activity of this family of compounds. This would be attractive because it would significantly shorten the synthetic sequence to a biologically useful compound.

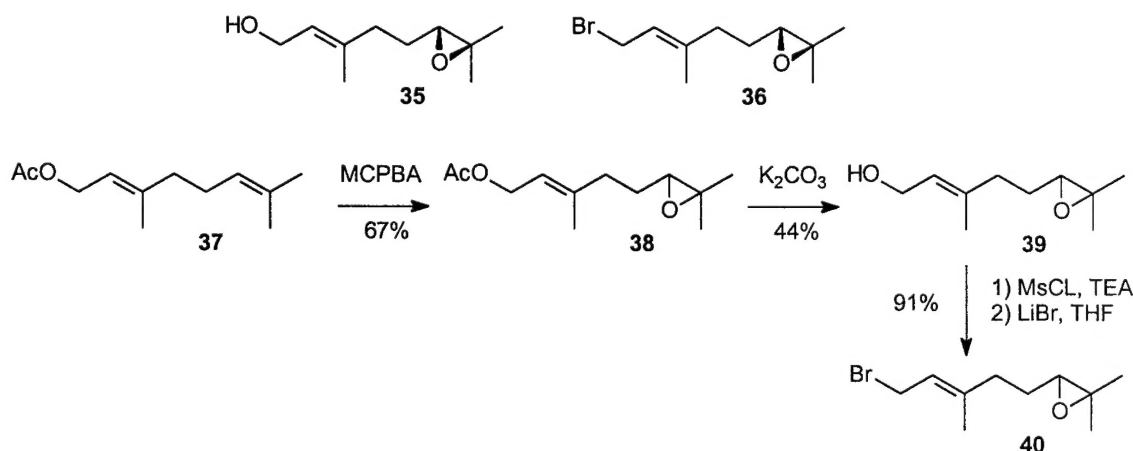


While most of our effort has been focused on developing the routes to Schweinfurthin B described above, we also have explored preparation of geraniol derivatives that would allow preparation of modified (unnatural) right halves. For these studies, the commercial dihydroxybenzoic acid **28** has been converted to the trimethyl derivative **29**, and then to the protected alcohol **30**. After treatment with *n*BuLi to induce directed ortho metallation, reaction with geranyl bromide (**31**) gave the geranylated



product **32** in reasonably good yield. Therefore, the oxidized geranyl bromide analogue **33** was prepared, and used in a parallel reaction. While we expect this strategy to afford the more highly oxidized compound **34**, complete characterization of this product is still underway.

Finally, we also have investigated preparation of nonracemic geraniol derivatives that ultimately may allow preparation of nonracemic schweinfurthins. The geranyl epoxide **35** has been prepared in nonracemic form⁴ and can be converted to the corresponding nonracemic bromide **36**.⁴ We have explored this transformation with racemic material as shown below, and prepared the racemic bromide **40**. In addition to establishing new methods for preparation of compound **36**, the more readily available bromide **40** will be used to explore procedures for linking this chain to the aromatic D-ring. If this material could be linked to the aromatic core through a variation of the procedures employed for synthesis of compound **32**, it should allow preparation of the nonracemic natural product, especially given that we have demonstrated control of the relative stereochemistry in formation of the tricyclic compound **23**. Therefore, our next step in this area will be to investigate this strategy for control of the absolute stereochemistry, leading to synthesis of nonracemic Schweinfurthin B.



Key Accomplishments.

- A cascade cyclization has been developed, as described in the original proposal, to provide an advanced tricyclic intermediate for assembly of racemic Schweinfurthin B with the desired relative stereochemistry.
- This tricyclic intermediate has been converted to an aldehyde and joined with a phosphonate representing the right half of the Schweinfurthins, to verify the strategy for joining the two subunits and to provide a protected form of dideoxy Schweinfurthin B.
- An alternate route to the tricyclic intermediate has provided an advanced bicyclic intermediate.
- The first steps in the proposed sequence to the nonracemic natural products have been explored with racemic material.
- One strategy for incorporation of functionality in the side chain, to allow attachment of dexamethasone, has been explored.

Reportable Outcomes.

Abstract: Studies directed at the total synthesis of Schweinfurthin B. J. D. Neighbors, E. M. Treadwell, and D. F. Wiemer, 36th Great Lakes Regional ACS Meeting, Minneapolis, MN, June, 2002. (see appendix)

Manuscript: A Cascade Cyclization Approach to Schweinfurthin B. Treadwell, E. M.; Neighbors, J. D.; Wiemer, D. F. *Org. Letters* **2002**, submitted. (Appendix)

PhD. Thesis: Edward M. Treadwell, PhD Thesis, University of Iowa, July 2001.

Degree Obtained: Edward M. Treadwell, PhD, University of Iowa

Employment Received: Edward M. Treadwell, Assistant Professor, Eastern Illinois University. Charleston, IL 61920.

Conclusions.

Substantial progress has been made toward synthesis of the natural product Schweinfurthin B. Even though we still hope to improve the yield of this reaction, we have demonstrated that an approach based on a cascade cyclization proceeds as we had proposed, and gives a key tricyclic intermediate with excellent control of the relative stereochemistry. The product of this reaction sequence already has been used to prepare the first synthetic analogue of the natural product in protected form, a compound that can be viewed as a dideoxy Schweinfurthin B (**27**). After one last transformation, removal of two protecting groups, we will send the final product to our collaborators at NIH for bioassays. If this compound shows any significant fraction of the biological activity of the natural product, it may be of use as a probe of the mechanism(s) responsible for the biological activity of this family of compounds and simplifies the synthesis. If it does not show activity, it highlights the importance of the A-ring functionality. Introduction of the two hydroxyl groups could be studied at the level of this stilbene, as well as in its left half precursors.

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1. Beutler, J. A.; Shoemaker, R. H.; Johnson, T.; Boyd, M. R. *J. Nat. Prod.* **1998**, *61*, 1509–1512.
2. Beutler, J. A. personal communication.
3. Treadwell, E. M.; Cermak, S. C.; Wiemer, D. F. *J. Org. Chem.* **1999**, *64*, 8718–8723
4. Corey, E. J.; Noe, M. C.; Shieh, W. C. *Tetrahedron Lett.* **1993**, *34*, 5995–5998.

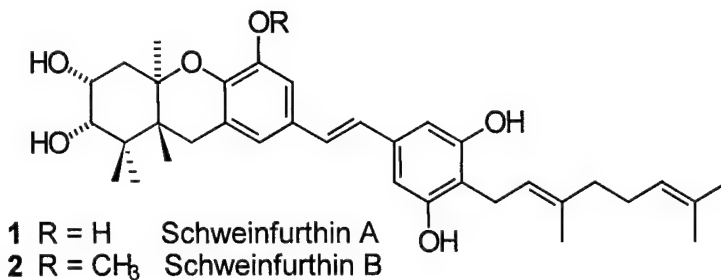
Appendices.

- 1) Abstract of a talk presented at the 36th Great Lakes Regional ACS Meeting, Minneapolis, MN, June, 2002. Studies directed at the total synthesis of Schweinfurthin B. J. D. Neighbors, E. M. Treadwell, and D. F. Wiemer.
- 2) Manuscript submitted to *Organic Letters* describing the cascade cyclization that leads to compound **23**.

STUDIES DIRECTED AT THE TOTAL SYNTHESIS OF SCHWEINFURTHIN B. *Jeffrey D.*

Neighbors, Edward M. Treadwell, David F. Wiemer. Department of Chemistry, University of Iowa, Iowa City, IA 52242-1294, fax: 319-335-1270

The schweinfurthins are a small set of prenylated stilbenes recently isolated from *Macaranga schweinfurthii*, and only three of the four isolated display significant anticancer activity. These three have a common "left-half" tricycle exemplified in the structures of schweinfurthins A (1) and B (2). We envision a late stage introduction of the stilbene olefin via HWE condensation and thus require a "left-half" tricyclic aldehyde to couple with our previously synthesized "right-half" synthon. A route involving the cationic cascade cyclization of a β -hydroxyselenide intermediate will be presented. It has been established that the phenylselenenyl moiety can be used to control the diastereoselectivity of this process.



A cascade cyclization approach to schweinfurthin B.

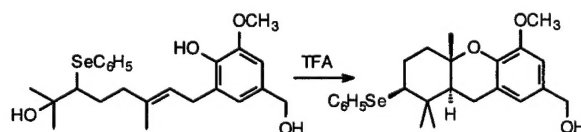
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Received Date (will be automatically inserted after manuscript is accepted)

ABSTRACT

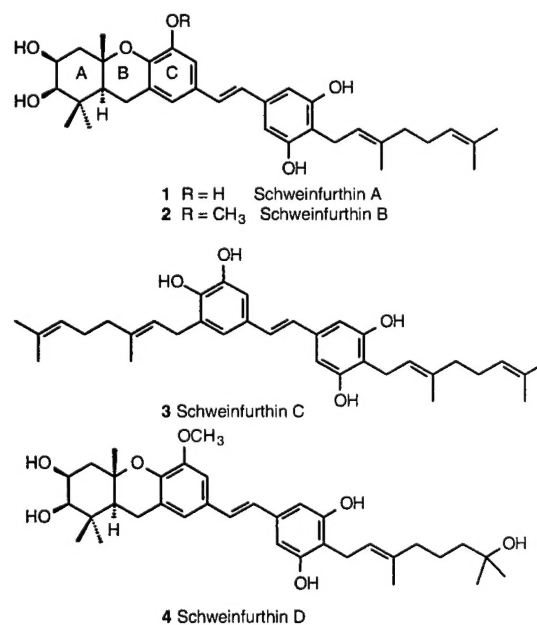


A strategy for synthesis of the hexahydroxanthene moiety of the natural products schweinfurthin A, B and D is described. The relative stereochemistry in the key cationic cyclization step is established through the preference of the phenylselenide substituent for an equatorial orientation.

The schweinfurthins (Figure 1, 1–4) are a small set of doubly prenylated stilbenes isolated from the African plant *Macaranga schweinfurthii* Pax. by Beutler *et al.* at the National Cancer Institute. Schweinfurthins A (1), B (2), and D (4) display significant activity in the NCI's 60-cell line anticancer assay with GI_{50} 's less than 0.5 μM .^{1,2} Their profile of activity does not match that of any clinically used anticancer agent, which suggests that these compounds may act either by a novel mechanism or at an unknown site. The schweinfurthins have been isolated in low and varying amounts from the natural source, and their absolute stereochemistry has yet to be elucidated. For these reasons, as well as their interesting biological activity, we have undertaken a total synthesis that ultimately should allow assignment of the schweinfurthins' absolute stereochemistry and provide a reliable source for further biological testing.

We have demonstrated the feasibility of a convergent approach to the schweinfurthins through synthesis of schweinfurthin C (3), the inactive congener.³ In that synthesis, the central stilbene olefin was prepared by a Horner-Wadsworth-

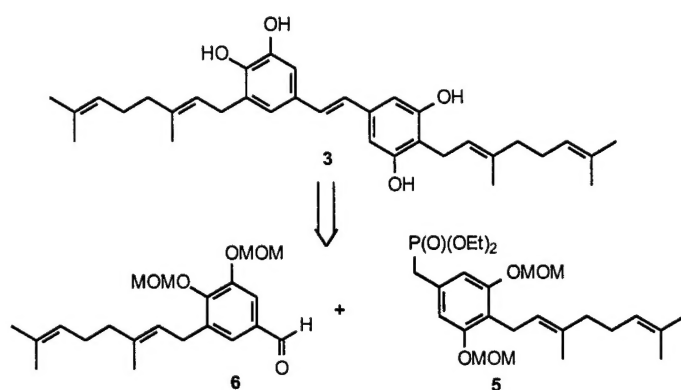
Emmons condensation of benzylic phosphonate 5 and aldehyde 6 (Scheme 1). The phosphonate was prepared in eight steps from commercially available 3,5-dihydroxybenzoic acid employing a directed



¹ Beutler, J. A.; Shoemaker, R. H.; Johnson, T.; Boyd, M. R. *J. Nat. Prod.* **1998**, *61*, 1509–1512.

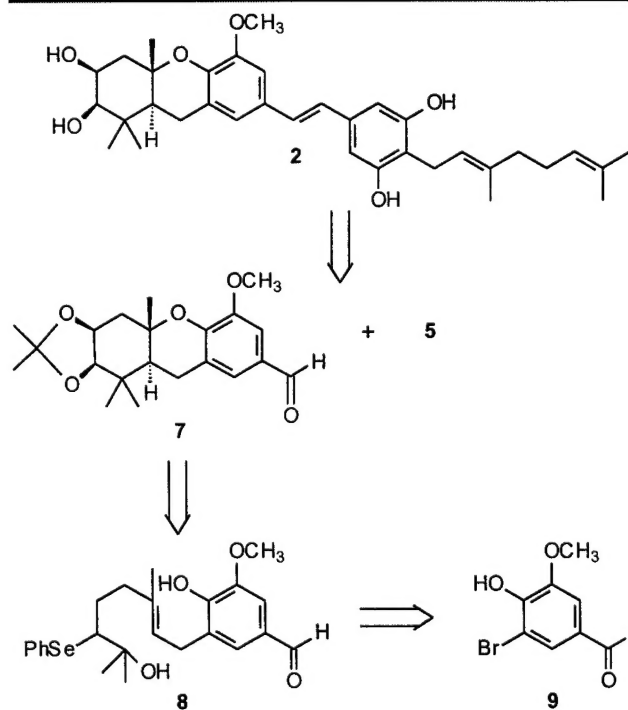
² Beutler, J. A.; Jato, J.; Cragg, G. M.; Boyd, M. R. *Nat. Prod. Lett.* **2000**, *14*, 399–404.

³ Treadwell, E. M.; Cermak, S. C.; Wiemer, D. F. *J. Org. Chem.* **1999**, *64*, 8718–8723, and references cited therein.



Scheme 1. Retrosynthetic analysis of schweinfurthin C.

ortho metalation for introduction of the geranyl substituent. Phosphonate **5** also could be used to advantage in preparation of the more complex schweinfurthins, provided preparation of a tricyclic aldehyde (**7**, Scheme 2) could be achieved. The methylated version of this tricyclic aldehyde was targeted initially because the requisite phenolic methyl ether could be carried along the sequence from the aromatic starting material, bromovanillin **9**.



Scheme 2. Retrosynthetic analysis of schweinfurthin B.

One approach to the hexahydroxanthene core could be based on an acid-catalyzed cyclization to assemble both the A- and B-rings on an aromatic C-ring in a single reaction. Previous reports on cyclizations of geranylated phenols are known, but often the cyclizations occurred in low yield with numerous byproducts observed.^{4,5} We hypothesized that a substituent α to the incipient carbocation could help stabilize the terminal cation,⁶ thereby possibly increasing the yield and providing an opportunity for stereocontrol. As shown in Figure 2, one transition state would place the phenylselenide substituent in an equatorial position with a pseudochair conformation in the incipient B-ring, while the other would require an axial phenylselenide group with a pseudoboat conformation. The use of hydroxyselenides for similar reactions has been described in two seminal papers by Kametani *et al.*, though application of the methodology to enantiopure material was not attempted.⁷ With this aim in mind, we envisioned the racemic β -hydroxyselenide **8** as a cyclization precursor that would allow evaluation of the viability of such an approach.

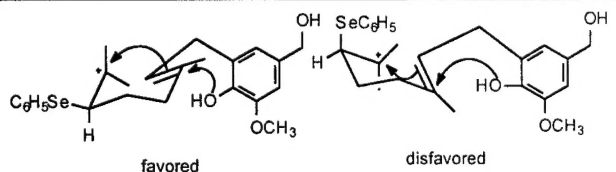


Figure 2. Possible transition states for cyclization of hydroxyselenide **8**.

The synthesis began with preparation of the known benzaldehyde derivative **10**⁸ from commercially available vanillin (Scheme 3). Reduction of the aldehyde and subsequent protection of the alcohol as the triethylsilyl ether afforded the fully protected arene **12**, and halogen-metal exchange followed by reaction with geranyl bromide allowed installation of the geranyl chain in 74% yield. An *m*CPBA epoxidation of compound **13** initially afforded a 1:1 mixture of the regioisomeric 6,7- and 2,3-epoxides in 55% yield along with the diepoxide (7%). Even though careful column chromatography could separate the two regioisomers, the low yield of the desired product was unattractive. When the reaction was conducted at lower temperatures with slow addition of the oxidant, the yield of the desired 6,7-epoxide **14** increased to 53% along with only 8% of the 2,3-epoxide and significant recovery of the

⁴ (a) Barua, A. K.; Banerjee, S. K.; Basak, A.; Bose, P. K. *J. Indian Chem. Soc.* **1976**, *53*, 638-639. (b) Manners, G.; Jurd, L.; Stevens, K. *Tetrahedron* **1972**, *28*, 2949-2959. (c) Trammell, G. L. *Tetrahedron Lett.* **1978**, 1525-1528.

⁵ Mechoulam and Yagen have reported cyclization of geranylolivetol in 88% yield but this required heating with conc. H_2SO_4 in nitromethane. Mechoulam, R.; Yagen, B. *Tetrahedron Lett.* **1969**, 5349-5352.

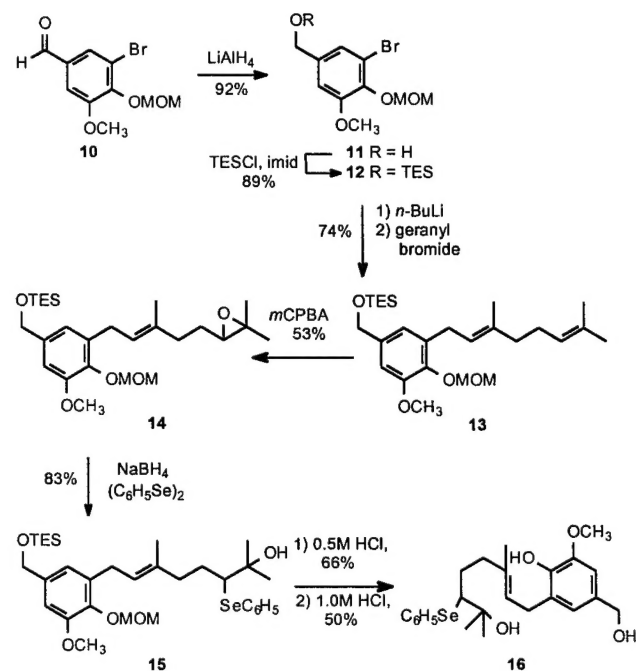
⁶ Stabilization of a similar cation by an adjacent phenylthio substituent has recently been reported. Branchaud, B. P.; Blanchette, H. S. *Tetrahedron Lett.* **2002**, *43*, 351-353.

⁷ (a) Kametani, T.; Suzuki, K.; Kurobe, H.; Nemoto, H. *J. Chem. Soc., Chem. Commun.* **1979**, 1128-1129. (b) Kametani, T.; Kurobe, H.; Nemoto, H.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1085-87.

⁸ Boger, D. L.; Jacobson, I. C. *J. Org. Chem.* **1991**, *56*, 2115-2122.

starting material (32%). Epoxide **14** reacted smoothly with phenylselenide anion generated *in situ*,⁹ to give the hydroxyselenide **15** in 83% yield.

Scheme 3. Initial synthesis of hydroxyselenide **16**.



The only transformations remaining prior to cyclization were removal of the two protecting groups, but in the best case scenario this was done through a two-step procedure. Initial treatment with 0.5 M HCl hydrolyzed the silyl ether and subsequent treatment with 1.0 M HCl hydrolyzed the MOM acetal in an overall yield of 33%. Despite numerous attempts, all efforts at removing both protecting groups in a single step gave either incomplete deprotection or lower yields with greater byproduct formation.

A second synthetic strategy was developed to address this problematic deprotection issue. Because the silyl ether could be readily removed, it appeared attractive to protect the phenolic functionality as a silyl ether as well. However, introduction of the phenolic silyl ether would have to follow the alkylation step in the synthetic sequence, because migration of the silyl group from the oxygen to the adjacent *ortho* carbon has been observed in similar reactions.¹⁰ Therefore an ethoxyethyl protected phenol was envisioned for the sequence up to and including the alkylation step, at which point it would be removed and a silyl ether installed in its place.¹¹

Direct protection of the phenol as the ethoxyethyl ether was not successful under acidic conditions, so an indirect route was employed. The

known alcohol **17**,¹² also available from vanillin, was disilylated and then selective cleaved to the free phenol **19** by treatment with 1.0 equivalent of tetrabutylammonium fluoride¹³ (Scheme 4). An acid-catalyzed reaction of compound **19** with ethyl vinyl ether gave the fully protected aryl bromide **20**. This intermediate can be prepared in multi-gram quantities in an overall yield of 68% from vanillin without need for a chromatographic separation. Application of the halogen-metal exchange protocol and reaction with geranyl bromide afforded the analogous geranylated arene, which upon acidic work-up gave the free phenol **21**. After silylation of the free phenol, the material was subjected to oxidation and epoxide opening analogous to that used on arene **13** delivered the protected α -hydroxyselenide **24**. The deprotected target **16** could be obtained in 84% yield by treatment of the disilylated material with excess TBAF.

To induce the desired cationic cyclization, the tertiary alcohol **16** was treated with acid under various conditions. Treatment of compound **16** with TFA afforded a single hexahydroxanthene system as the labile trifluoroacetate **25**. Purification of this product by column chromatography gave both the trifluoroacetate **25** and the parent alcohol **26** in 43% combined yield.

The relative stereochemistry of the hexahydroxanthene was assigned after extensive NMR spectroscopy on the trifluoroacetate **25**. Analysis of the coupling constants observed for the C-2 hydrogen (schweinfurthin numbering) suggested an axial disposition and hence an equatorial orientation for the phenylselenide group. The bridgehead methine hydrogen (C-9a) also appeared to be in an axial orientation based on analysis of the coupling constants with the benzylic hydrogens at C-9. In this case, a COSY spectrum nicely displayed the H-9_{ax}, H-9_{eq}, H-9a spin system, indicative of a

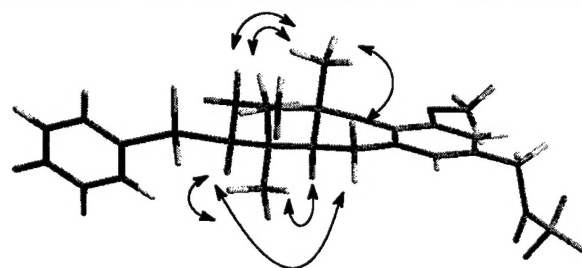


Figure 3. Selected NOESY correlations for compound **25** shown on a SPARTAN minimized structure (PM3 level).

trans-decalin skeleton. Furthermore, the chemical shifts of the methyl groups compared favorably to those reported for a related *trans*-fused system, but did not agree with those of a related *cis*-fused structure.¹⁴ Finally, a NOESY spectrum revealed correlations (Figure 3) of the bridgehead methyl

⁹ Sharpless, K. B.; Lauer, R. F. *J. Am. Chem. Soc.* **1973**, *95*, 2697–2699.

¹⁰ When treated with *n*-butyllithium both compound **18** and the TIPS analog show a 1,3 O-C silyl migration in the only isolable products.

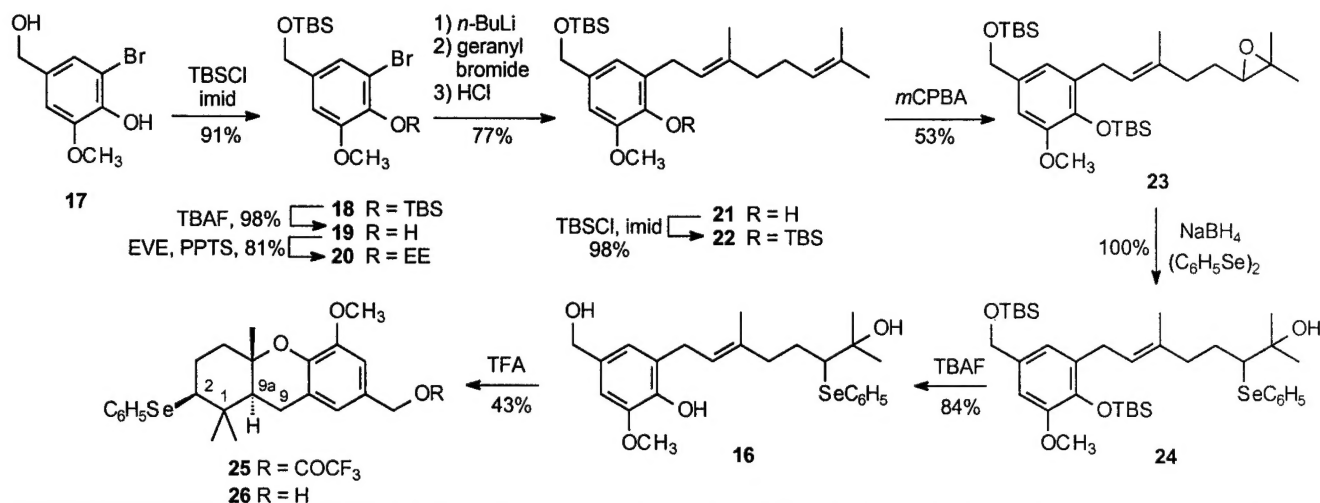
¹¹ The EE group was not carried throughout the sequence to avoid introduction of diastereomers and because the phenolic EE group was readily cleaved upon silica-gel column chromatography.

¹² a) Brink, M. *Acta Chem. Scand.* **1965**, *19*, 255–256. (b) Claus, P.; Schilling, P.; Gratzl, J. S.; Kratzl, K. *Monatsh. Chem.* **1972**, *103*, 1178–1193.

¹³ Collington, E. W.; Finch, H.; Smith, I. J. *Tetrahedron Lett.* **1985**, *26*, 681–684.

¹⁴ Rouessac, A.; Rouessac, F. *Tetrahedron* **1987**, *37*, 4165–4170.

Scheme 4. Revised synthesis of hydroxyselenide **16**.



group with axial hydrogens at C-3 and C-9 and to the axial methyl group at C-1. On the other face of the molecule, complementary correlations were observed between the equatorial methyl group at C-1 and the axial hydrogen at C-9a, as well as from the axial hydrogen at C-2 to both the C-1 equatorial methyl group and the C-9 equatorial hydrogen.

The NMR data make clear that the phenylselenide substituent was successful in providing a single diastereomer of the hexahydroxanthene and may facilitate the cyclization. The equatorial disposition of the phenylselenide moiety in the final product is encouraging in that this single substituent appears to effectively govern the stereochemistry of the bridgehead centers, as expected from consideration of the transition states (Figure 2).

Preparation of the tricycle **26** should allow elaboration of racemic schweinfurthin B after introduction of the A-ring hydroxyl groups and coupling with phosphonate **5**. Alternatively, now that the viability of this cyclization strategy has been shown, preparation of the epoxide **23** in nonracemic form should allow preparation of nonracemic schweinfurthin B (**2**). Our efforts to prepare the nonracemic epoxide, as well as to complete preparation of the natural products themselves, will be reported in due course.

Acknowledgement. Financial support from the DOD Breast Cancer Research Program (DAMD17-01-1-0276 and DAMD17-02-1-0423) is gratefully acknowledged.

Supporting Information Available: Experimental procedures and spectral data for compounds **16** to **26**. This material is available free of charge via the Internet at <http://pubs.acs.org>.